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Le analisi di sottogruppo negli studi clinici

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Analisi di sottogruppo

Nelle analisi di sottogruppo, il campione di pts arruolati nello studio viene suddiviso in un certo numero di sottogruppi (definiti secondo le caratteristiche basali dei pts arruolati nello studio) per verificare se l'effetto del trattamento (per uno specifico endpoint dello studio) è "diverso" nei diversi sottogruppi.

1- Wang NEJM 2007

Analisi di sottogruppo

Nel momento in cui il clinico si trova a dover applicare i risultati di uno studio al trattamento del singolo paziente

i risultati delle analisi di sottogruppo potrebbero rappresentare per il medico la base su cui individualizzare (personalizzare) il trattamento.

Ambivalence

‘Subgroups kill people’

van Gijn J. Extrapolation of trial data into practice: where is the limit? Cerebrovasc Dis 1995; 5: 159–62.

‘Not doing subgroup analyses has very probably killed more people.’

Rothwell PM. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation Lancet 2005; 365: 176–86.

Analisi di sottogruppo:
vengono sempre riportate negli studi clinici controllati randomizzati?

Credibility of claims of subgroup effects in randomised controlled trials: systematic review

TRIALS	No. (%)
Included in this analysis	409
Reporting subgroup analysis	**207 /409 (=44%)**
Claiming subgroup effect	83/207 (=41%)
Claiming subgroup effect for the primary outcome	**64/207 (=31%)**
	
Reporting in the methods that they did a test of interaction	32/64 (=50%)
Reporting “p value” or information to calculate the “p value”	20/32

Sun Y, BMJ 2012

BOLERO-2 (Ph III): Everolimus in Advanced BC

24 Countries, 196 sites

N = 724

- **Postmenopausal ER+,HER2-**
- **Advanced BC** (unresectable LABC or MBC)
- **NSAI refractory disease**:

recurrence during or within 12 mo after the end of adjuvant treatment

or

progression during or within 1 mo after the end of treatment for advanced disease

R
2:1

EVE 10 mg daily
+
EXE 25 mg daily (n = 485)

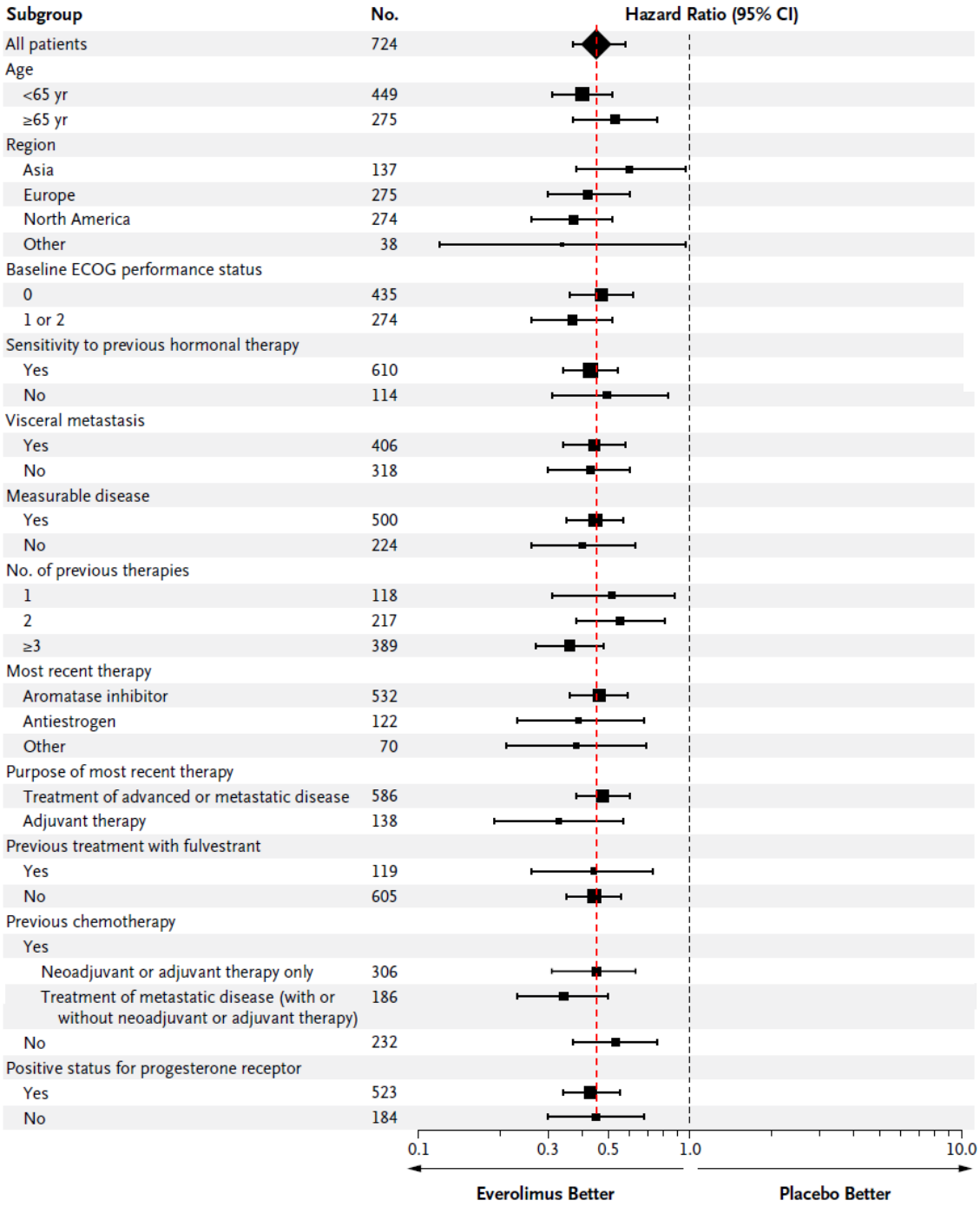
Placebo
+
EXE 25 mg daily (n = 239)

Endpoints

- **Primary:** PFS (local assessment)
- **Secondary:** OS, ORR, QOL, safety, bone markers, PK

Abbreviations: BC, breast cancer; ER+, estrogen receptor-positive; EVE, everolimus; EXE, exemestane; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Ph, phase; PK, pharmacokinetics; QOL, quality of life.

Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.



BOLERO 2

PFS benefits were consistent in all subgroups

Baselga J et al. NEJM 2012;366:520-9

I risultati delle analisi di sottogruppo possono dare informazioni più o meno affidabili per essere trasferite nella pratica clinica…..

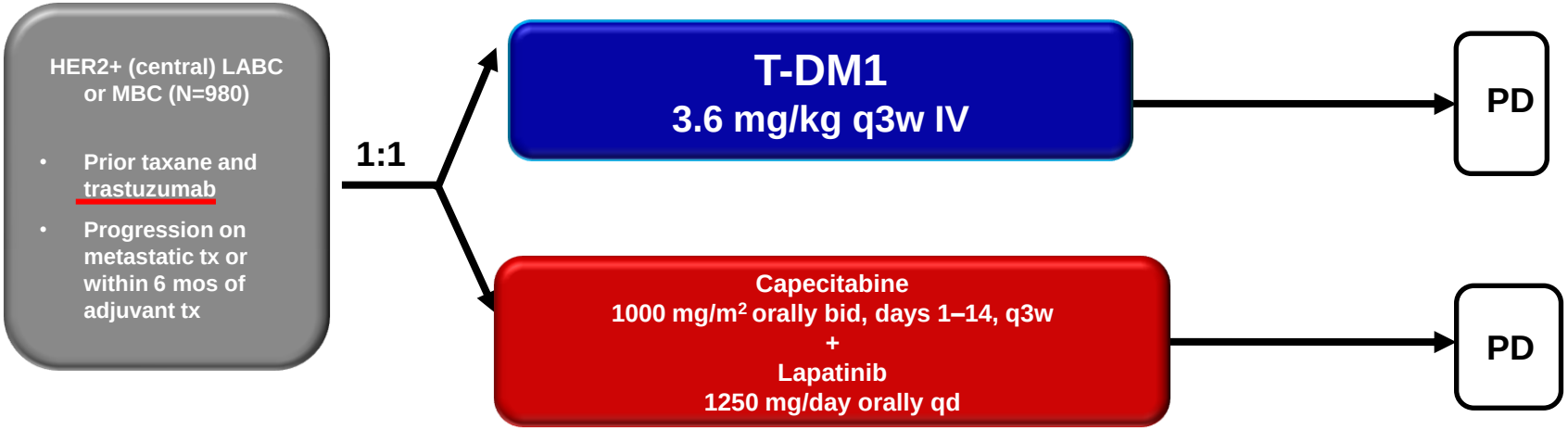
- Problematiche di tipo metodologico
- Problematiche di tipo statistico

ANALISI PER SOTTOGRUPPI

- **Rappresentatività del campione originale?**
- **Rischio di risultato falsamente positivo.**
- **Molteplicità**
- ***Reporting bias***
- **Test di interazione**
- ***Pre-specified Vs pre-planned***

EMILIA trial (Phase III)

- **EMILIA Study Design**



- **Primary endpoints:** PFS by independent review, OS, and safety

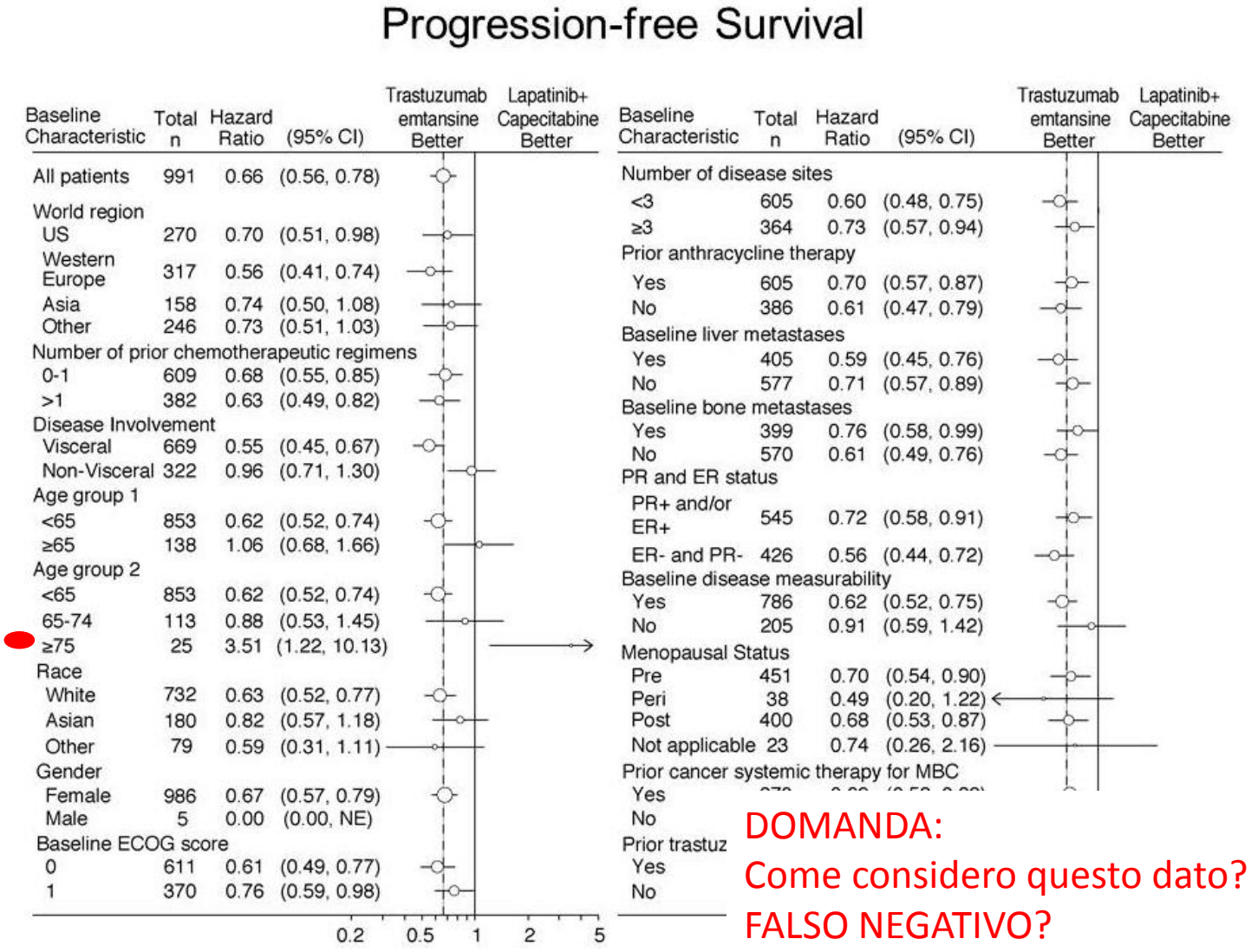
Outcome	T-DM1	Lap +Cap	HR (95%CI); p value
Median PFS	9.6 mo	6.4 mo	0.65 (0.55-0.77); p <.001
Median OS	30.9 mo	25.1 mo	0.68 (0.55-0.85); p <.001

- **Rate of grade 3-4 AEs** lower with T-DM1 vs Lapatinib+Capecitabine (41% vs 57%)

Verma S, NEJM 2012; 367:1783-91

Ancillary analyses

EMILIA trial :Subgroup Analyses of Progression-Free Survival per IRC Assessment



DOMANDA:
Come considero questo dato?
FALSO NEGATIVO?

Assessment report
EMA/749228/2013

Analisi di sottogruppo:
come dovrebbero essere riportate?

Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses

Xin Sun,[1 2] Matthias Briel,[1 3] Stephen D Walter,[1] Gordon H Guyatt[1 4]

BMJ 2010;340:c117

Clinical and policy decision making always involves uncertainty. It is unlikely that a subgroup claim will meet either all or none of our criteria—in almost all instances, a subgroup claim will meet some but not all the criteria.

Criteria to assess the credibility of subgroup analyses

Design

- Is the subgroup variable a characteristic measured at baseline or after randomisation?*
- Is the effect suggested by comparisons within rather than between studies?
- Was the hypothesis specified a priori?
- Was the direction of the subgroup effect specified a priori*
- Was the subgroup effect one of a small number of hypothesised effects tested?

Analysis

- Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?
- Is the significant subgroup effect independent?*

Context

- Is the size of the subgroup effect large?
- Is the interaction consistent across studies?
- Is the interaction consistent across closely related outcomes within the study?*
- Is there indirect evidence that supports the hypothesised interaction (biological rationale)?

Forest plot and interpretation of subgroups

Cuzick J, Lancet 2005

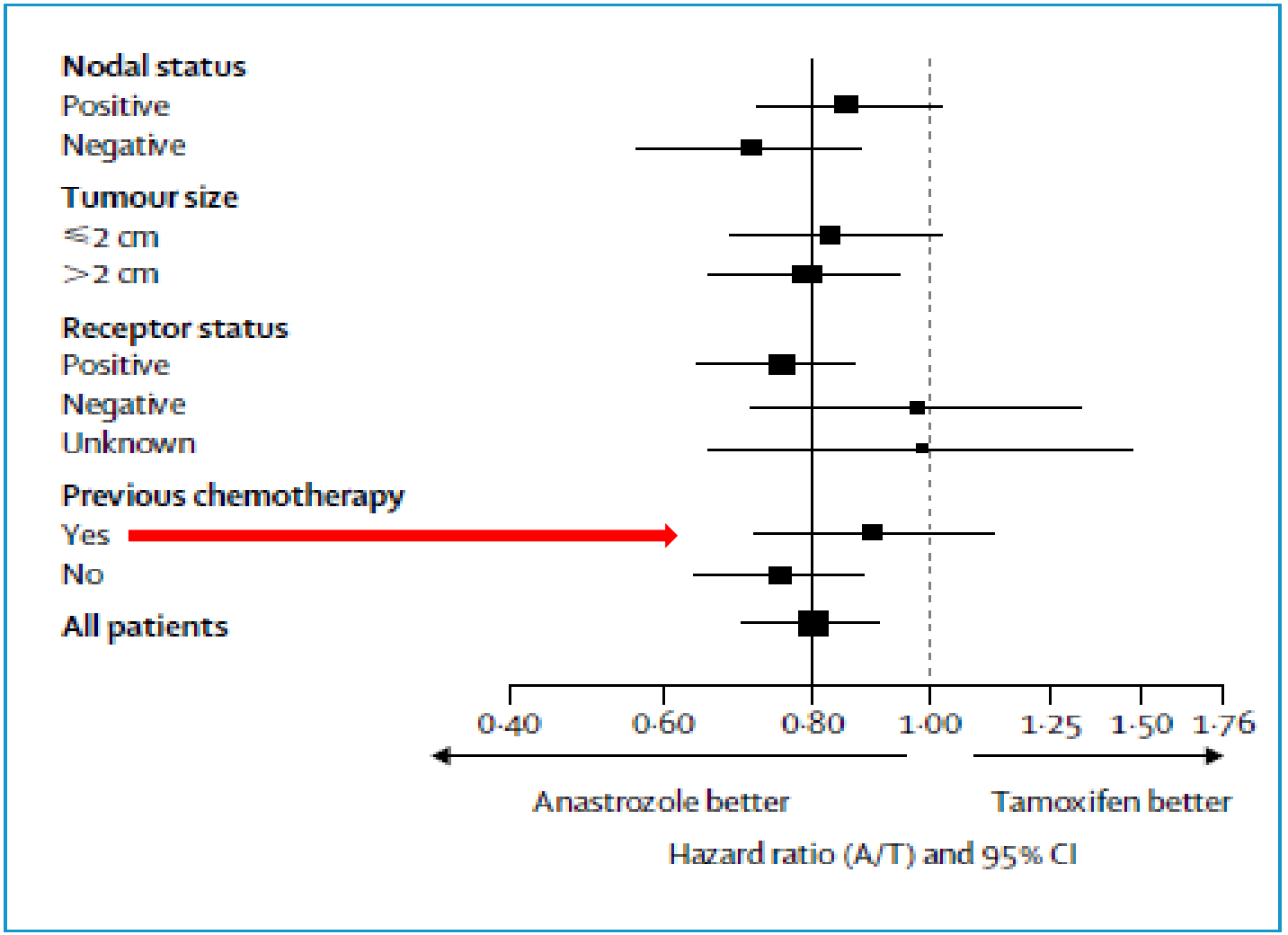


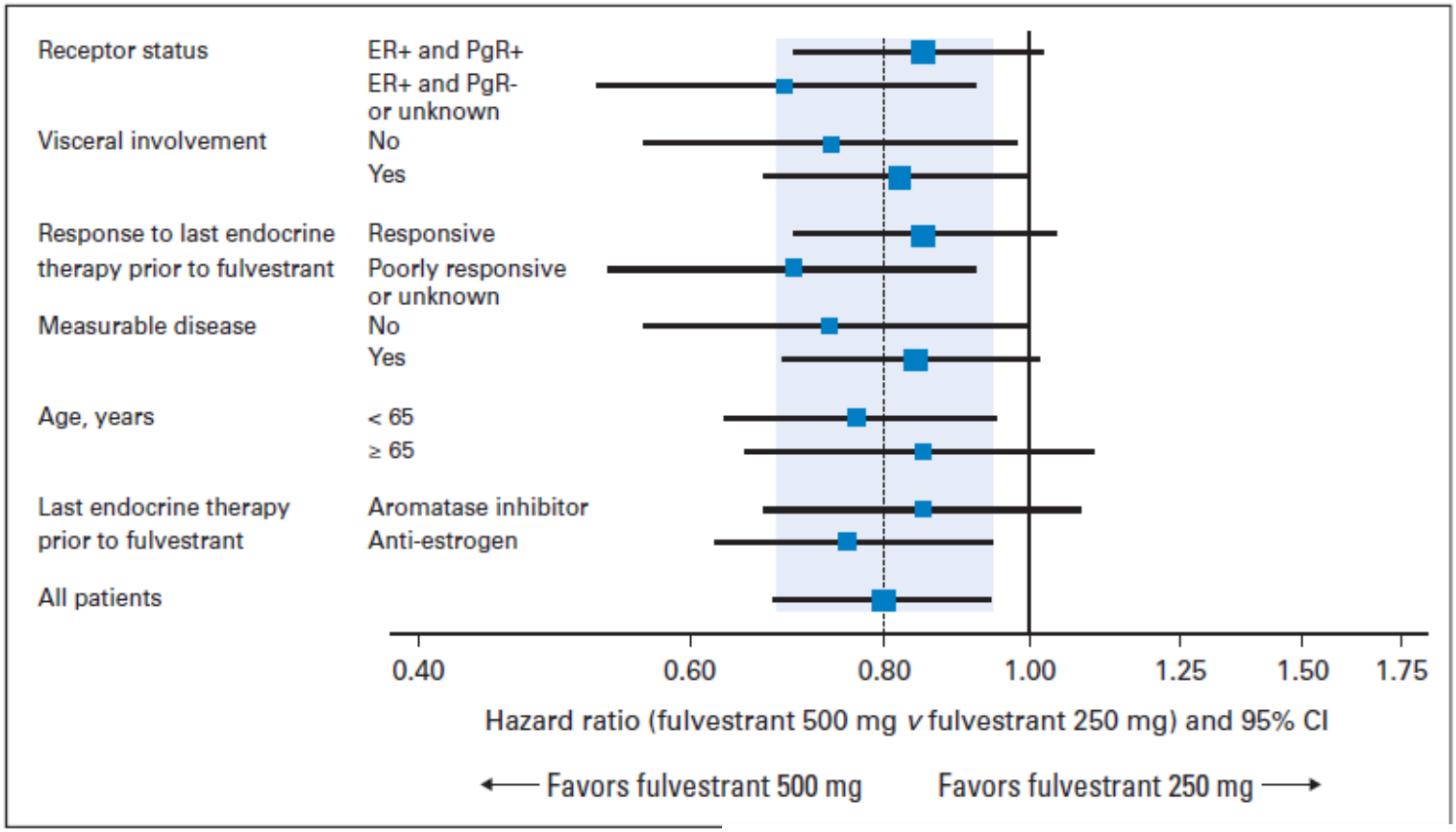
Figure: **Suggested modification as applied to time to recurrence in subgroups of the ATAC trial[3]**

Dotted line shows no effect point, and (new) bold line shows overall treatment effect point.

Results of the CONFIRM Phase III Trial Comparing Fulvestrant 250 mg With Fulvestrant 500 mg in Postmenopausal Women With Estrogen Receptor–Positive Advanced Breast Cancer

Di Leo A, JCO 2010

Fig.3 –The PFS forrest plot according to the predefined covariates.



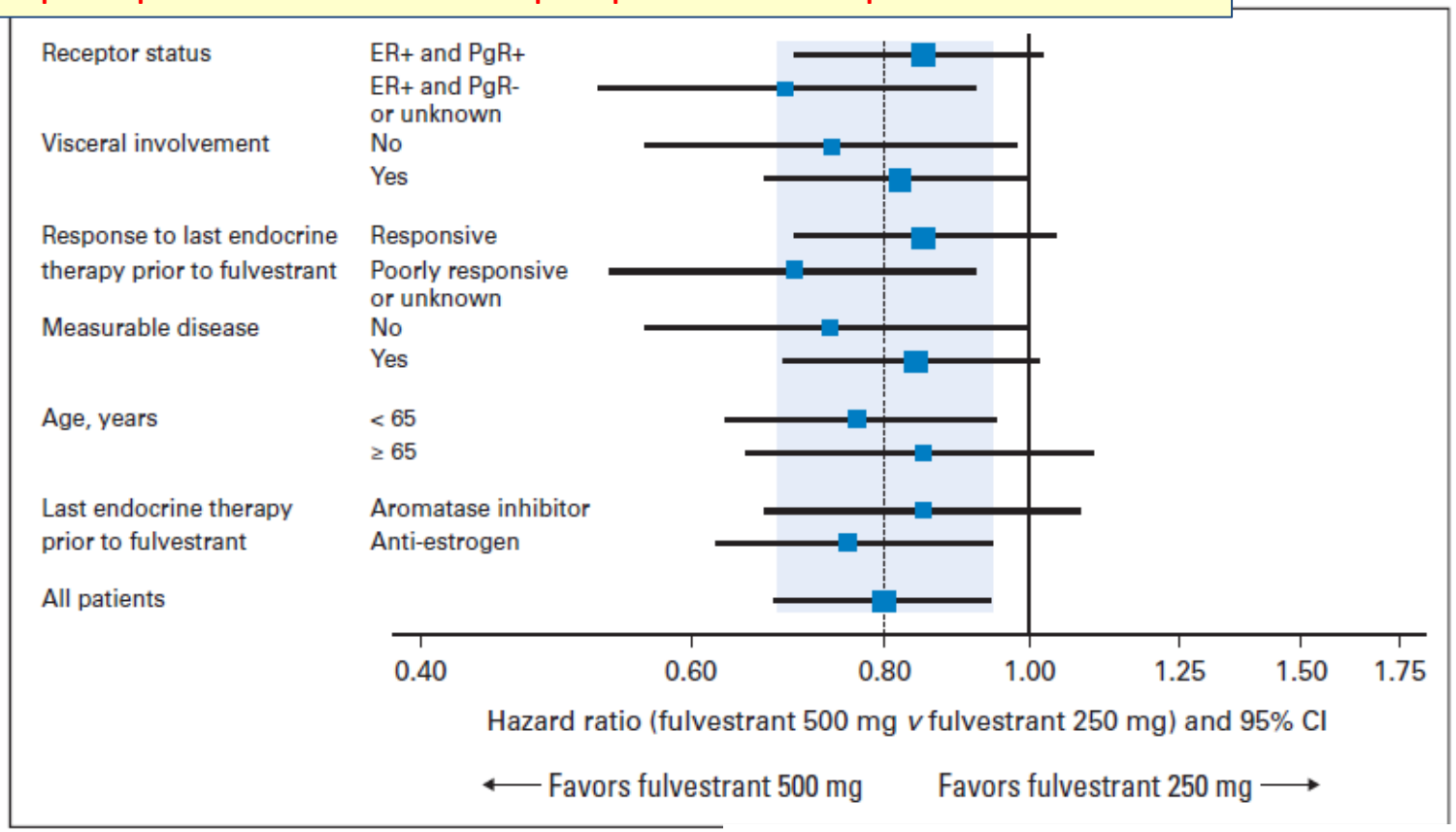
The PFS analysis adjusted by predefined covariates resulted in an HR of 0.78 (95% CI, 0.67 to 0.92; $P = .003$). Figure 3 shows the PFS forest plot according to the predefined covariates and shows that the treatment effect seems to be consistent across all subgroups.

Results of the CONFIRM Phase III Trial Comparing Fulvestrant 250 mg With Fulvestrant 500 mg in Postmenopausal Women With Estrogen Receptor–Positive Advanced Breast Cancer

Di Leo A, JCO 2010

Fig.3 –The PFS forrest plot according to the predefined covariates.

Analisi “pre-specificate” ma non “ pre-pianificate”: quale differenza?



The PFS analysis adjusted by predefined covariates resulted in an HR of 0.78 (95% CI, 0.67 to 0.92; $P = .003$). Figure 3 shows the PFS forest plot according to the predefined covariates and shows that the treatment effect seems to be consistent across all subgroups.

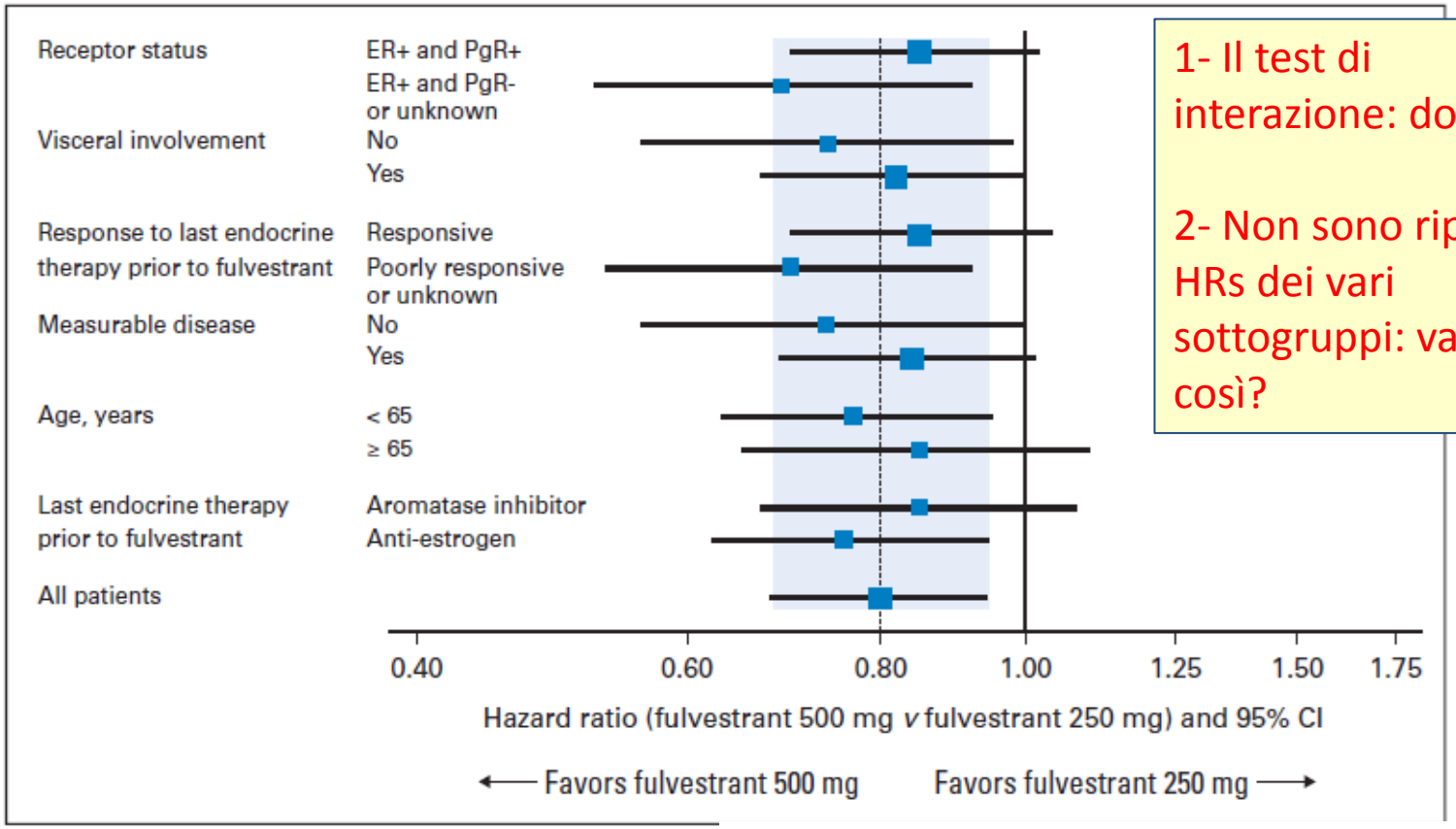
ANALISI PER SOTTOGRUPPI

- **Post-hoc**
  - "Fishing Expedition"…
- **Pre-specified** (preannunciata)
  - fattore di stratificazione? test di interazione?
  - (in ogni caso) è solo generazione di ipotesi
- **Pre-planned** (pre-pianificata)
  - definizione di un piano statistico
    - hierarchical approach
    - alpha-spending (tra confronto primario e sottogruppi di interesse)
    - adeguamento delle dimensioni campionarie
  - "superamento" della generazione di ipotesi

Results of the CONFIRM Phase III Trial Comparing Fulvestrant 250 mg With Fulvestrant 500 mg in Postmenopausal Women With Estrogen Receptor–Positive Advanced Breast Cancer

Di Leo A, JCO 2010

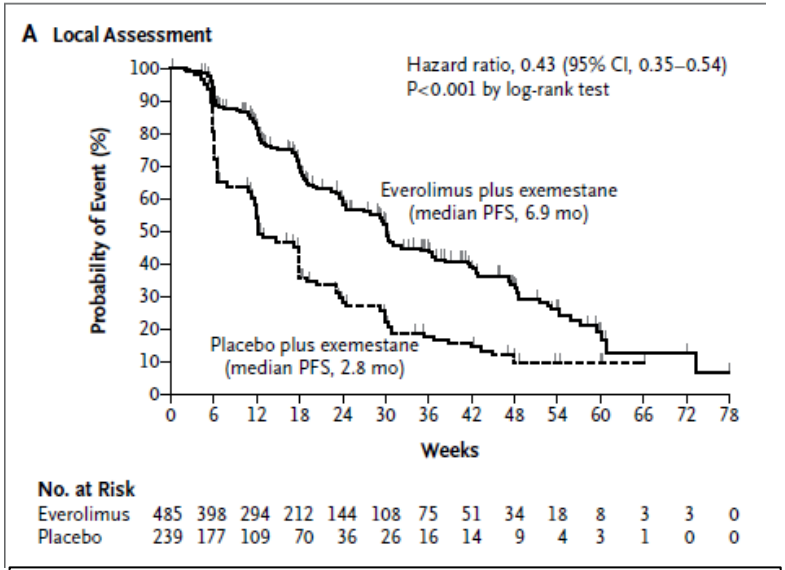
Fig.3 –The PFS forrest plot according to the predefined covariates.



1- Il test di interazione: dov'è?

2- Non sono riportati HRs dei vari sottogruppi: va bene così?

The PFS analysis adjusted by predefined covariates resulted in an HR of 0.78 (95% CI, 0.67 to 0.92; $P = .003$). Figure 3 shows the PFS forest plot according to the predefined covariates and shows that the treatment effect seems to be consistent across all subgroups.



PFS by local assessment

The results for progression-free survival were also consistent across all subgroups (Fig. 2).

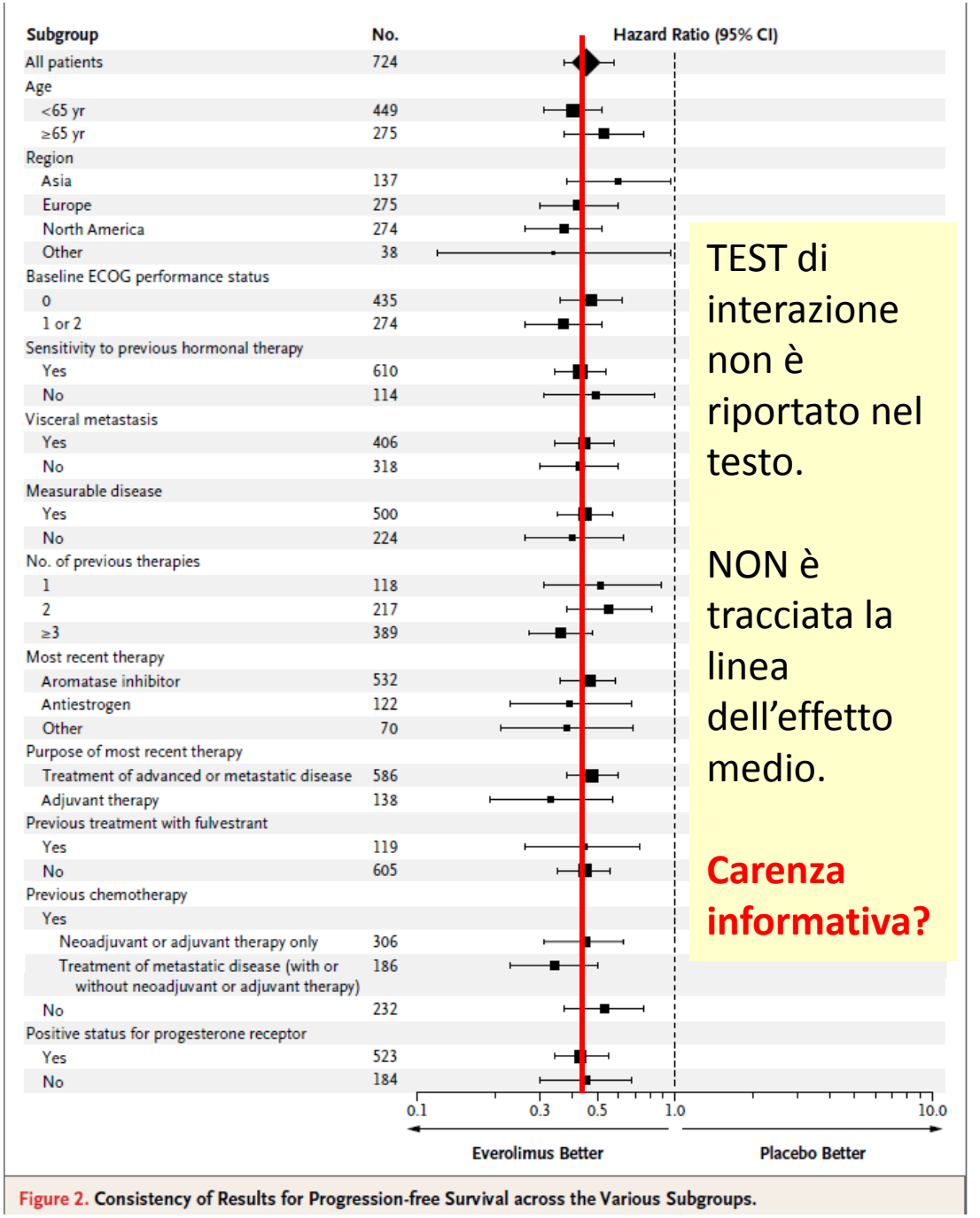


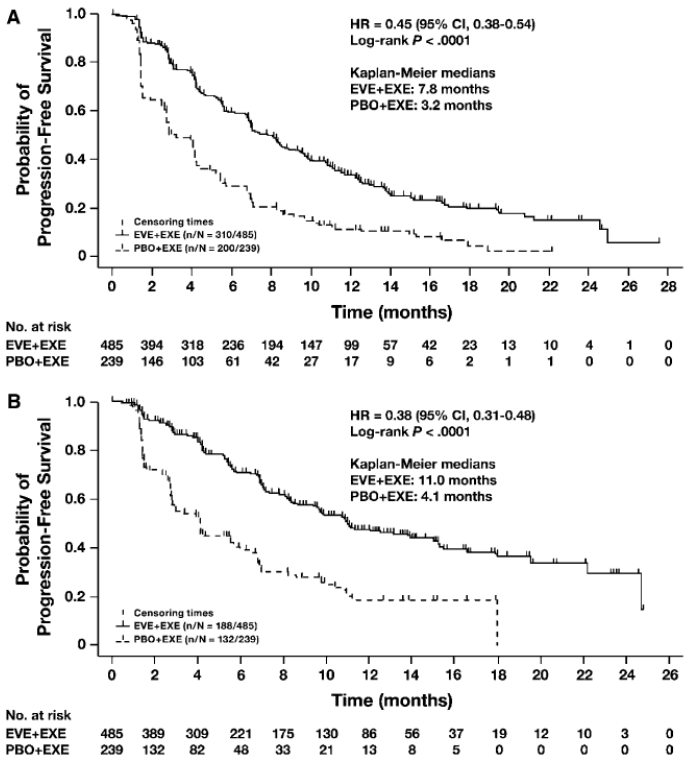
Figure 2. Consistency of Results for Progression-free Survival across the Various Subgroups.

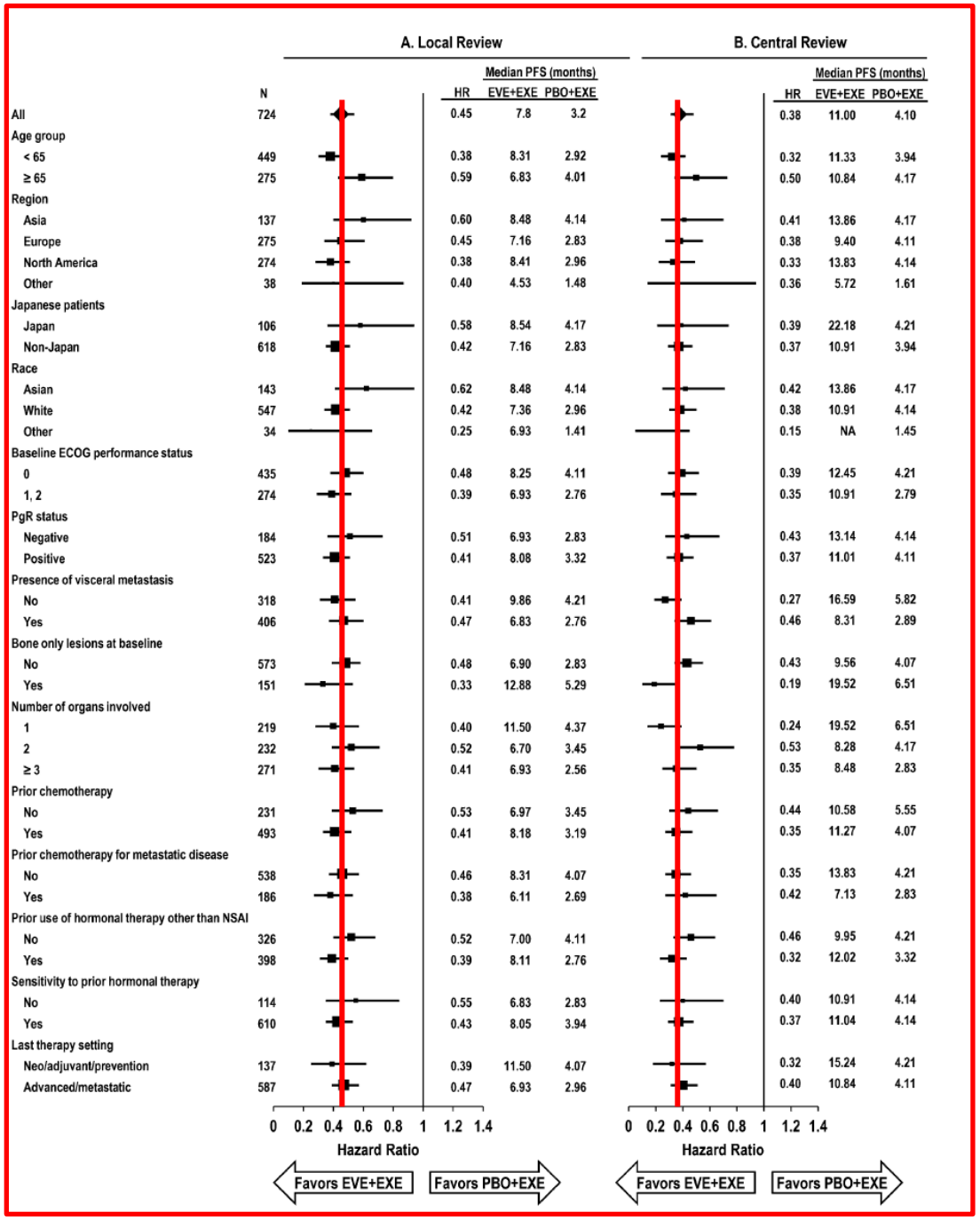
TEST di interazione non è riportato nel testo.

NON è tracciata la linea dell'effetto medio.

Carenza informativa?

Baselga J, NEJM 2012

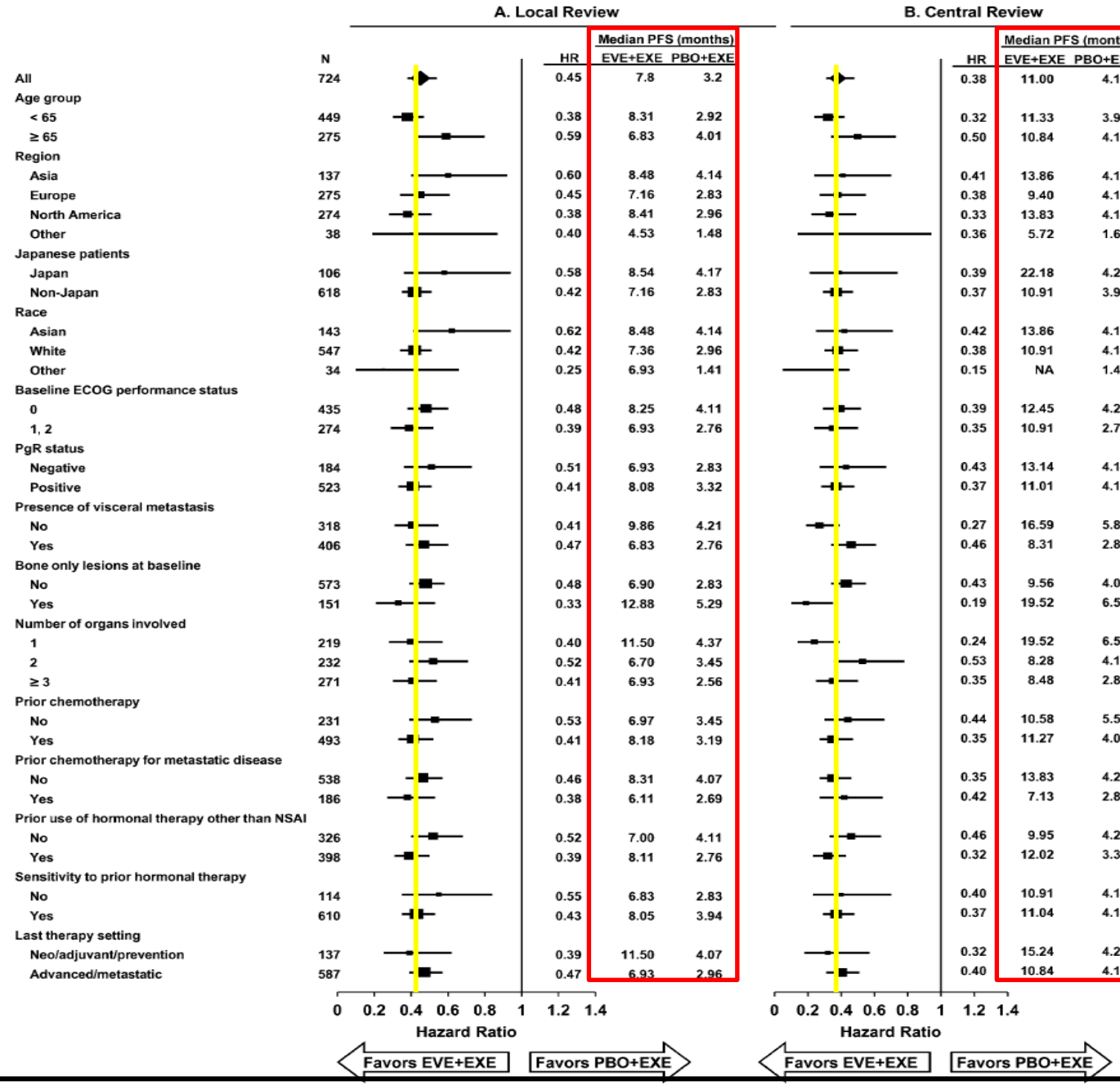




BOLERO 2

PFS at median f up of 17.7 mo

Yardley DA , Adv Ther 2013



!!
These are the median PFS value and no the IC 95% of HRs.

E' corretto presentare i risultati delle analisi di sottogruppo in questo modo?

Yardley DA, Adv Ther 2013

A- Analisi di sottogruppo ed impatto sulla pratica clinica

ATAC trial

post-, hormone-sensitive , EBC pts treated with Surgery± RT± Chemotherapy

Random 1:1:1 x 5 y

- **Anastrozole 1 mg +placebo**
- **Tamoxifen 20 mg +placebo**
- **Anastrozole 1 mg +Tamoxifen 20 mg**

Primary endpoints: DFS, tolerability
Secondary endpoints: Contralateral BC, TTR, OS

From 1996 to 2000 were enrolled 9366 pts (84% HR+)

Median f up: 68 months
ANA>TAM in DFS

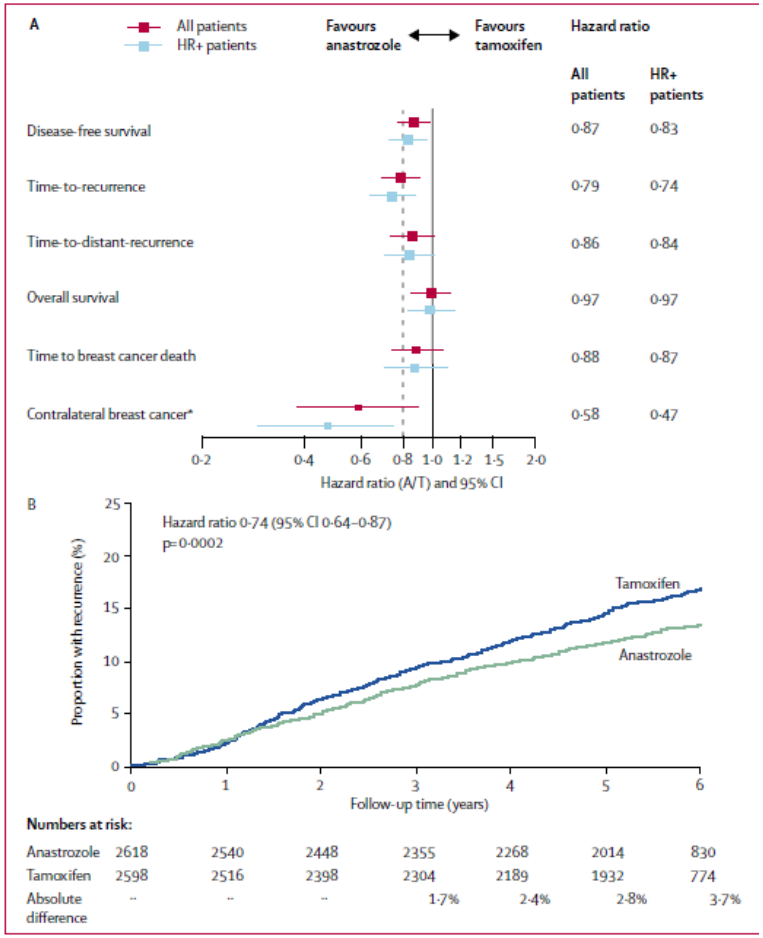


Figure: (A) Efficacy endpoints for all patients and hormone-receptor-positive patients and (B) time-to-recurrence in hormone-receptor-positive patients

ATAC Trialists' Group. Lancet 2005; 365:60-62

Retrospective Analysis of Time to Recurrence in the ATAC Trial According to Hormone Receptor Status: An Hypothesis-Generating Study

	No. of Patients	Breast Cancer Events						
		A		T		A *v* T		
		No.	%	No.	%	HR	95% CI	*P*
ER+/PgR+	5,709	191	10	222	12	0.84	0.69 to 1.02	.07
ER+/PgR−	1,372	50	11	102	24	0.43	0.31 to 0.61	< .0001
ER−/PgR+	220	17	27	25	33	0.79	0.43 to 1.47	.5
ER−/PgR−	703	66	28	79	32	0.90	0.65 to 1.25	.5
ER+/PgRuk	518	22	13	20	11	1.29	0.71 to 2.37	.4
ERuk/PgRuk	743	46	19	47	19	0.96	0.64 to 1.44	.8
Other	101							
Totals	9,366	402	12.9	498	16.0	0.79	0.70 to 0.90	.0005

Dowsett M, JCO 2005; 23:7512-17

Retrospective Analysis of Time to Recurrence in the ATAC Trial According to Hormone Receptor Status: An Hypothesis-Generating Study

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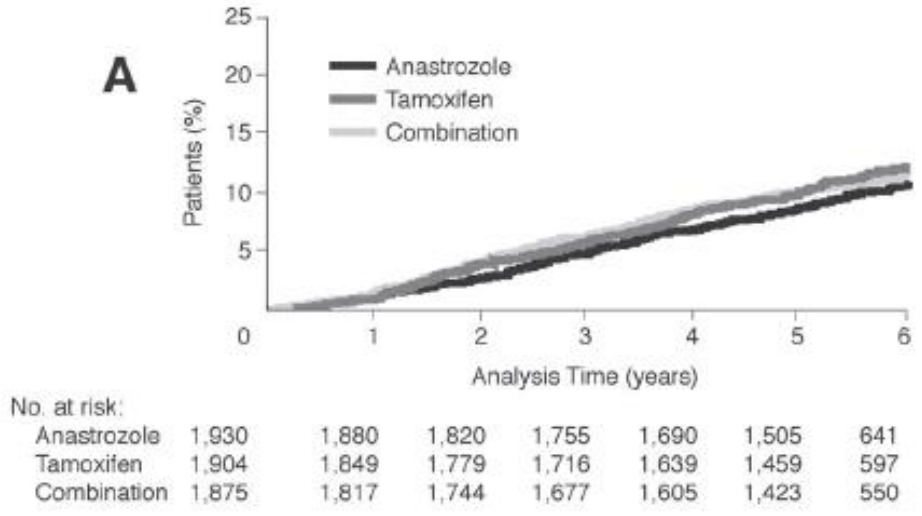
test of interaction between the three categories of PgR status (positive, negative, unknown) and treatment for ER+ disease was highly significant ($P = .0004$).

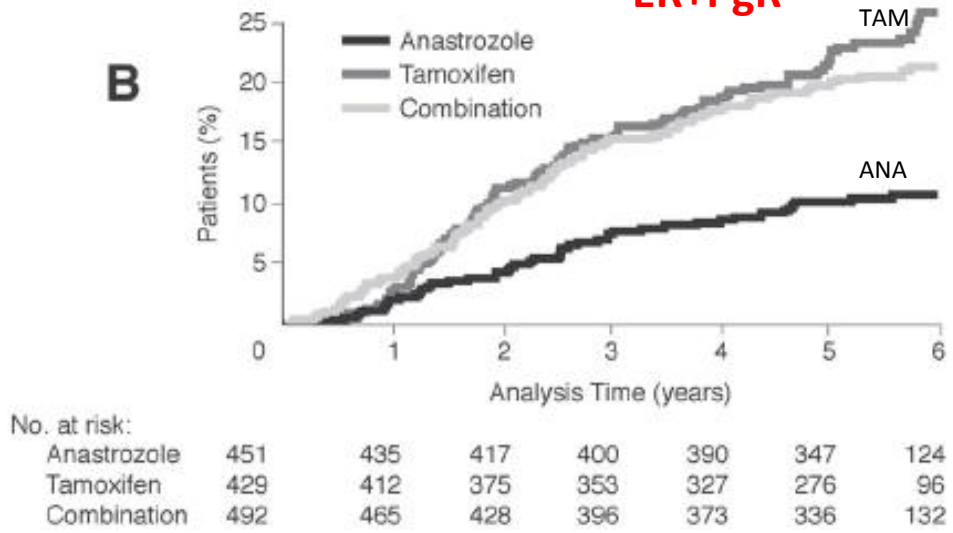
Dowsett M, JCO 2005; 23:7512-17

Retrospective Analysis of Time to Recurrence in the ATAC Trial According to Hormone Receptor Status: An Hypothesis-Generating Study

ER+PgR+



ER+PgR-



Time To Recurrence (TTR) in the ER+/PgR+ and the ER+/PgR- patient subgroups at a median follow up of 68 months.

HR data from Case Record Forms (CRFs)

Dowsett M, JCO 2005; 23:7512-17

Retrospective Analysis of Time to Recurrence in the ATAC Trial According to Hormone Receptor Status: An Hypothesis-Generating Study

Dowsett M, JCO 2005; 23:7512-17

The *P* values should be interpreted with caution because of the retrospective nature of the analysis with the generation of multiple subgroups.

	No. of Patients	Breast Cancer Events						
		A		T		A *v* T		
		No.	%	No.	%	HR	95% CI	*P*
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Other	101							
Totals	9,366	402	12.9	498	16.0	0.79	0.70 to 0.90	.0005

Questo "p value": è giusto che venga riportato?

Relationship Between Quantitative Estrogen and Progesterone Receptor Expression and Human Epidermal Growth Factor Receptor 2 (HER-2) Status With Recurrence in the Arimidex, Tamoxifen, Alone or in Combination Trial

Purpose
To determine the relationship between quantitative estrogen-receptor (ER) and progesterone-receptor (PgR) expression and human epidermal growth factor 2 (HER-2) status with time to recurrence (TTR) in postmenopausal women with hormone receptor–positive primary breast cancer treated with anastrozole or tamoxifen as adjuvant therapy.

Patients and Methods
Formalin-fixed, paraffin-embedded tumor blocks were retrospectively collected from patients in the monotherapy arms of the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial and centrally tested for ER, PgR and HER-2. ER and PgR were scored using continuous scales and HER-2 was scored as 0 to 3+ with 2+ cases being analyzed by fluorescence in situ hybridization.

Results
Blocks were collected from 2,006 of 5,880 eligible patients. Tissue was assessable and ER and/or PgR positivity confirmed centrally in 1,782 cases. In these, TTR was longer for anastrozole than for tamoxifen by a similar extent to that in the overall trial. None of the three biomarkers identified a set of patients with differential benefit from anastrozole over tamoxifen. Patients with low ER, low PgR, and high HER-2 expression had a poorer prognosis with either drug. Only 2.6% of patients in the highest quartile of PgR experienced recurrence after 5 years, compared with 13.2% in the lowest quartile.

Conclusion
Quantitative expression of ER and PgR and HER-2 status did not identify patients with differential relative benefit from anastrozole over tamoxifen: TTR was longer for anastrozole than for tamoxifen in all molecular subgroups. Low ER or PgR or high HER-2 expression are associated with a high risk of recurrence with either anastrozole or tamoxifen.

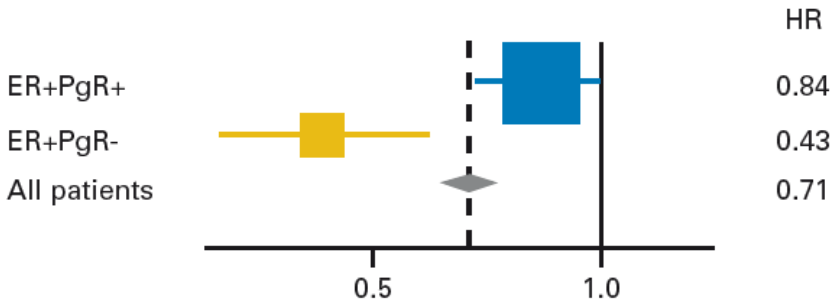
Dowsett M, JCO 2008; 26:1059-65

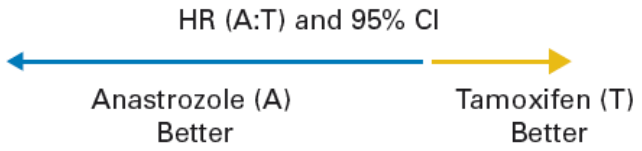
Relationship Between Quantitative Estrogen and Progesterone Receptor Expression and Human Epidermal Growth Factor Receptor 2 (HER-2) Status With Recurrence in the Arimidex, Tamoxifen, Alone or in Combination Trial

Mitch Dowsett, Craig Allred, Jill Knox, Emma Quinn, Janine Salter, Chris Wale, Jack Cuzick, Joan Houghton, Norman Williams, Elizabeth Mallon, Hugh Bishop, Ian Ellis, Denis Larsimont, Hironobu Sasano, Pauline Carder, Antonio Llombart Cussac, Fiona Knox, Valerie Speirs, John Forbes, and Aman Buzdar

J Clin Oncol 26:1059-1065. © 2008 by American Society of Clinical Oncology

Determinazioni eseguite perifericamente sull'intero campione di 9366 pazienti





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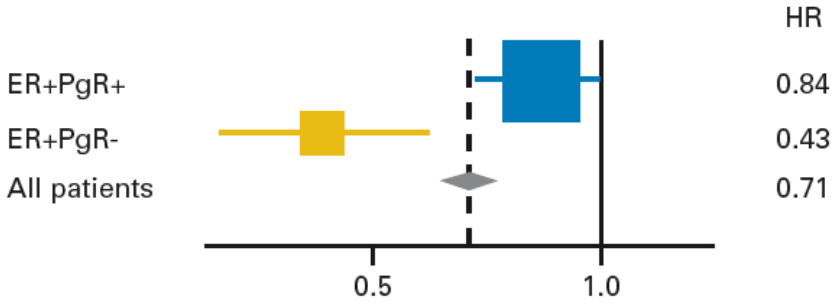
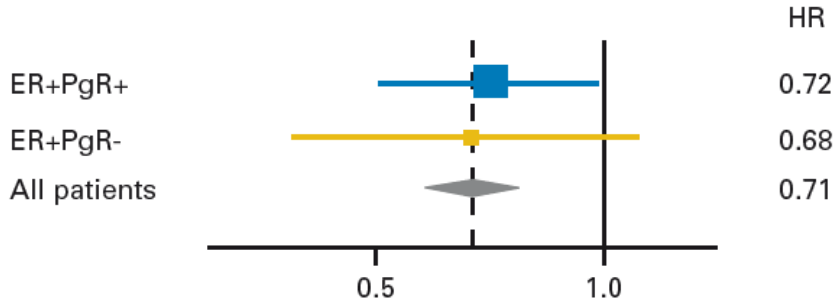
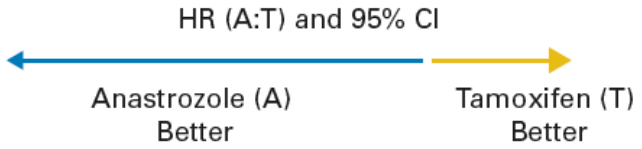
J Clin Oncol 26:1059-1065. © 2008 by American Society of Clinical Oncology

Determinazioni eseguite perifericamente sull'intero campione di 9366 pazienti



Determinazioni eseguite centralmente su un sottogruppo di 1782 pazienti





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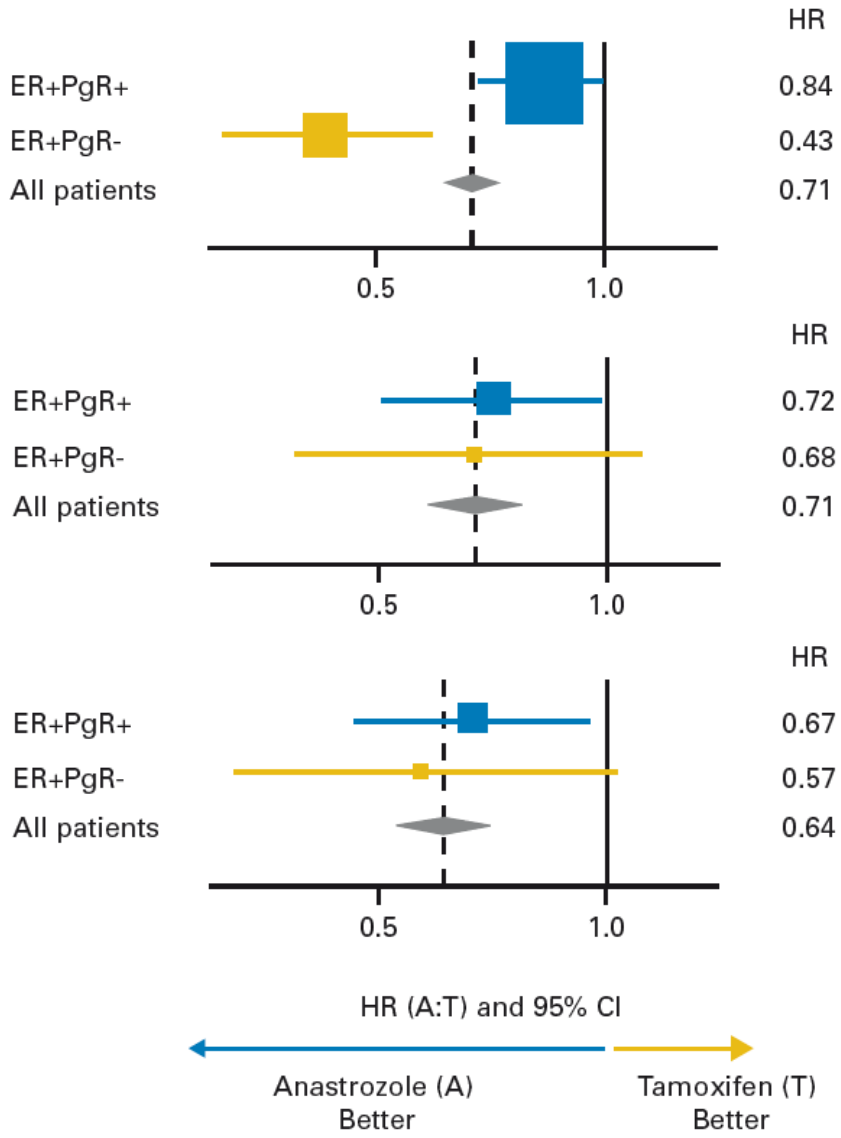
Determinazioni eseguite perifericamente sull'intero campione di 9366 pazienti

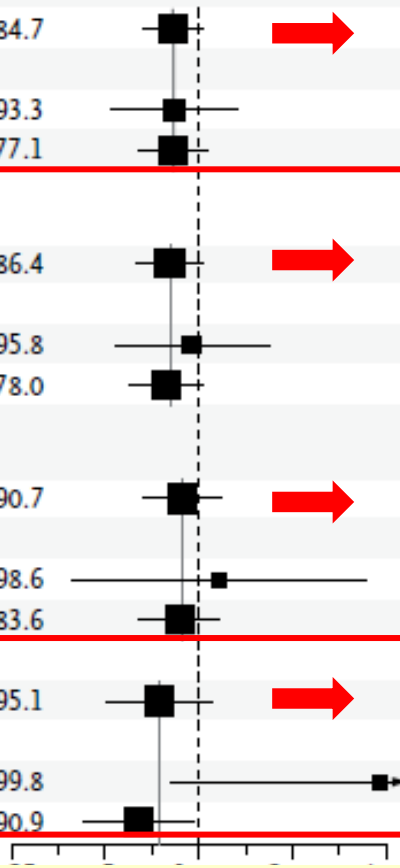
Determinazioni eseguite centralmente su un sottogruppo di 1782 pazienti

Determinazioni eseguite perifericamente sullo stesso sottogruppo di 1782 pazienti



B End Points, Overall and According to Chemotherapy Cohort

End Point	No. of Patients		No. of Patients with Event		5-Yr Rate (%)		Hazard Ratio (95% CI)	P Value
	Tamoxifen–OS	Tamoxifen	Tamoxifen–OS	Tamoxifen	Tamoxifen–OS	Tamoxifen		
Disease-free survival								
All patients	1015	1018	139	160	86.6	84.7	0.83 (0.66–1.04)	0.10
Prior chemotherapy								
No	473	476	32	38	93.4	93.3	0.83 (0.52–1.34)	0.96
Yes	542	542	107	122	80.7	77.1	0.82 (0.64–1.07)	
Freedom from breast cancer								
All patients	1015	1018	120	140	88.4	86.4	0.81 (0.63–1.03)	0.09
Prior chemotherapy								
No	473	476	23	24	95.1	95.8	0.95 (0.54–1.69)	0.54
Yes	542	542	97	116	82.5	78.0	0.78 (0.60–1.02)	
Freedom from distant recurrence								
All patients	1015	1018	89	96	91.3	90.7	0.88 (0.66–1.18)	0.40
Prior chemotherapy								
No	473	476	7	6	98.7	98.6	1.16 (0.39–3.44)	0.62
Yes	542	542	82	90	84.8	83.6	0.87 (0.64–1.17)	
Overall survival								
All patients	1015	1018	47	59	96.7	95.1	0.74 (0.51–1.09)	0.13
Prior chemotherapy								
No	473	476	8	2	99.2	99.8	3.84 (0.81–18.08)	0.03
Yes	542	542	39	57	94.5	90.9	0.64 (0.42–0.96)	



Quale differenza c'è tra il "p value" rosso e il "p value" celeste?
Se il "p value" rosso è significativo, cosa SIGNIFICA?
Se il "p value" celeste è significativo, cosa SIGNIFICA?

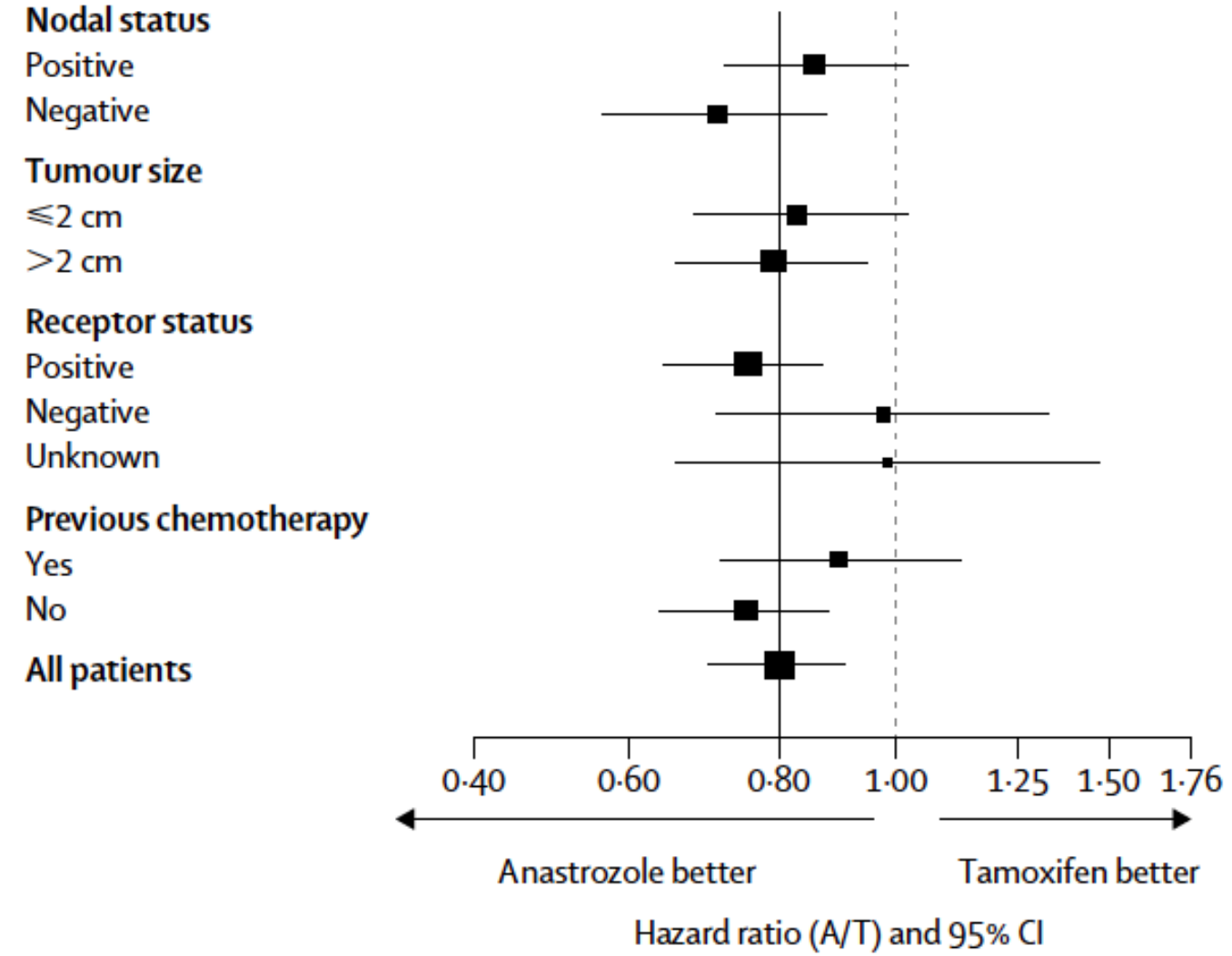
Il test di interazione …

- Se significativo, indica che "*l'efficacia relativa del trattamento è significativamente* ***diversa*** *tra i sottogruppi considerati*"

- **Non indica** se quanto osservato in ciascuno dei sottogruppi è statisticamente significativo
- E' solo la maniera migliore per dimostrare che c'è una **ipotesi** che vale la pena di verificare prospetticamente

Forest plots and the interpretation of subgroups

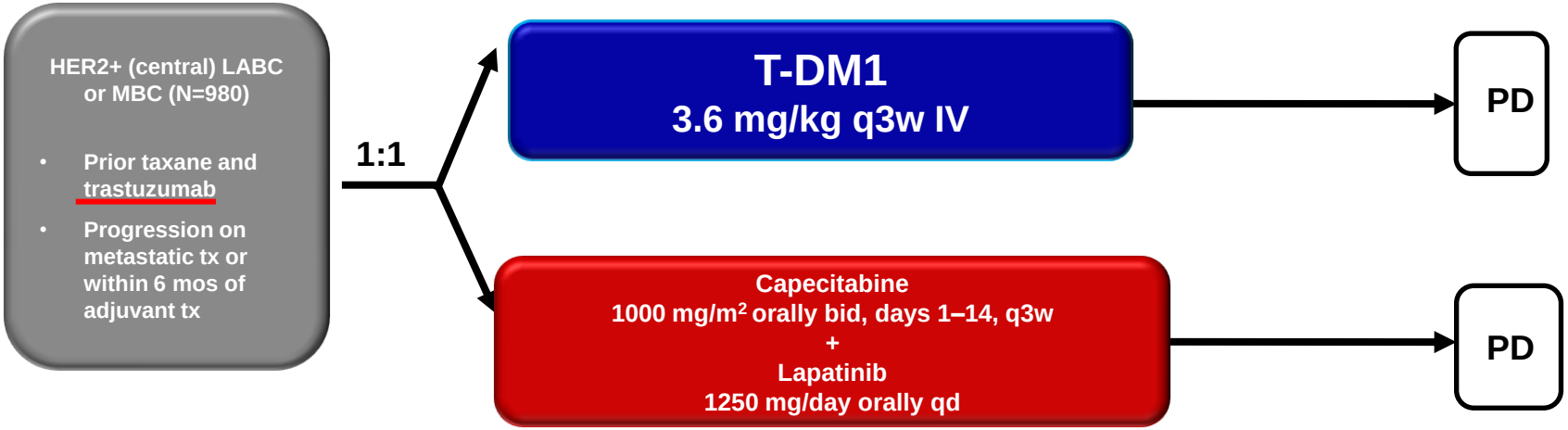
Jack Cuzick www.thelancet.com Vol 365 April 9, 2005



B- Gli enti regolatori e le analisi di sottogruppo

EMILIA trial (Phase III)

- **EMILIA Study Design**



- **Primary endpoints:** PFS by independent review, OS, and safety

Outcome	T-DM1	Lap +Cap	HR (95%CI); p value
Median PFS	9.6 mo	6.4 mo	0.65 (0.55-0.77); p <.001
Median OS	30.9 mo	25.1 mo	0.68 (0.55-0.85); p <.001

- **Rate of grade 3-4 AEs** lower with T-DM1 vs Lapatinib+Capecitabine (41% vs 57%)

Verma S, NEJM 2012; 367:1783-91

Verma S, NEJM 2012; 367:1783-91

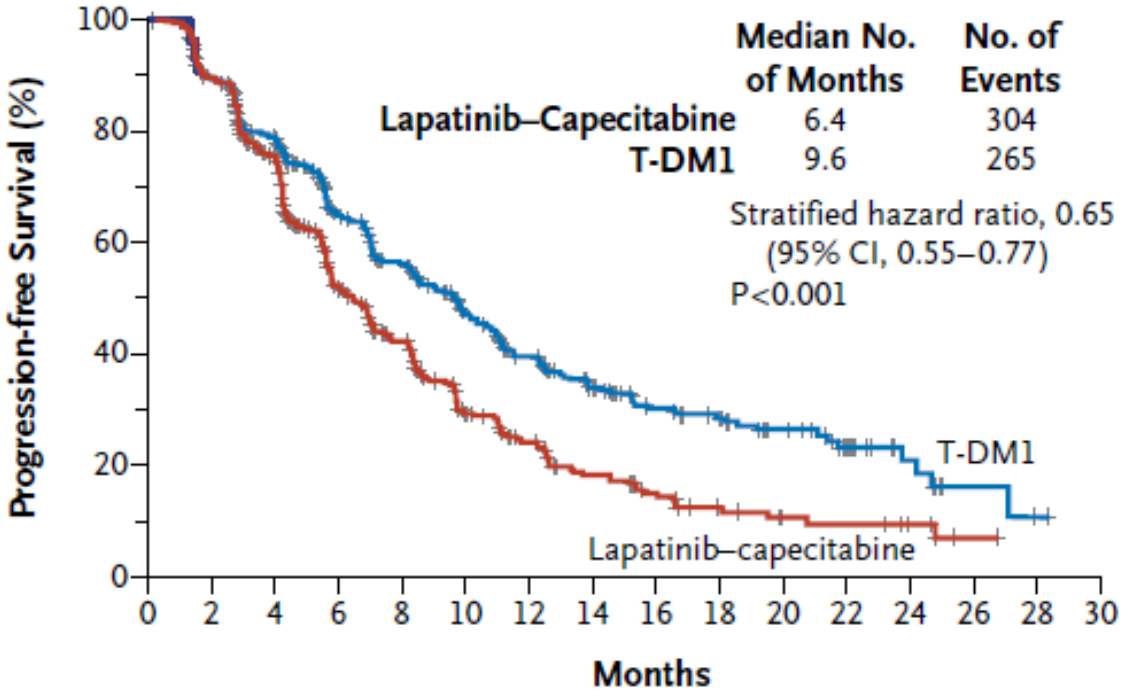
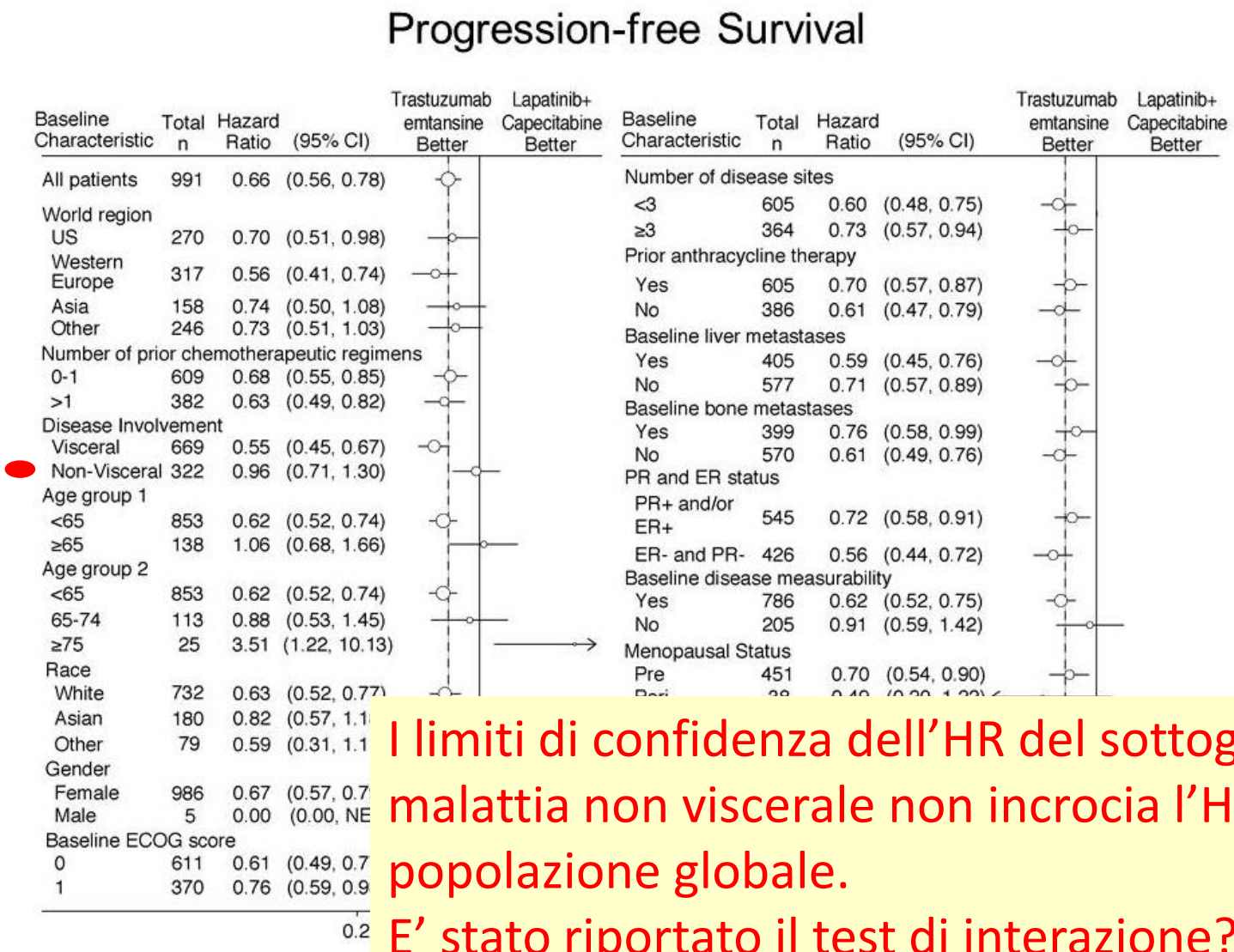


Figure 1. Progression-free Survival, as Assessed by an Independent Review Committee.

Nell'EPAR per il T-DM1 (2013), EMA ha riportato che un beneficio consistente del trattamento con T-DM1 è stato osservato nella maggioranza dei sottogruppi pre-specificati valutati, supportando la robustezza dei risultati dello studio EMILIA.

Ancillary analyses

EMILIA trial :Subgroup Analyses of Progression-Free Survival per IRC Assessment



I limiti di confidenza dell'HR del sottogruppo malattia non viscerale non incrocia l'HR della popolazione globale.

E' stato riportato il test di interazione?

Assessment report
EMA/749228/2013

EMILIA trial

Non-visceral disease

There was a less impressive effect in patients with non-visceral disease, and a similar finding was seen for pertuzumab (data not shown). However, this was based solely on the study site classification at the time of randomization for which explicit guidance had not been provided (the applicant had expectations that sites/investigators had adequate knowledge of visceral and non-visceral disease definitions). The sites of disease involvement have been subsequently reviewed according to IRC data, and further PFS (based on IRC assessments, data cut-off 14 January 2012) and OS (data cut-off 31 July 2012) subgroup analyses have been conducted using baseline IRC tumor assessments and applying the following two definitions of visceral disease (a) vs. non-visceral disease (b):

Definition 1: a) Presence of disease in the lungs or liver (either target or non- target lesions) vs. b) absence of disease in both the lungs and liver

Definition 2: a) Presence of disease in the lungs or liver or ascites or pleural effusion (either target or non-target lesions) vs. b) absence of disease in all these 4 sites

When the IRC data are used and the revised classifications applied, a benefit of trastuzumab emtansine compared with lapatinib plus capecitabine was observed for patients with disease that did not involve visceral organs.

EPAR

- I dati su cui si basa una AS devono essere affidabili.
- Poiché la definizione di m. viscerale e NON viscerale non era omogenea nei singoli centri, EMA ha fatto eseguire l' analisi dopo una riclassificazione della malattia viscerale e malattia non viscerale.
- Quanto mi posso fidare di una riclassificazione ed analisi post-hoc?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2014
EMA/CHMP/632090/2014
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[1] (initial authorisation)

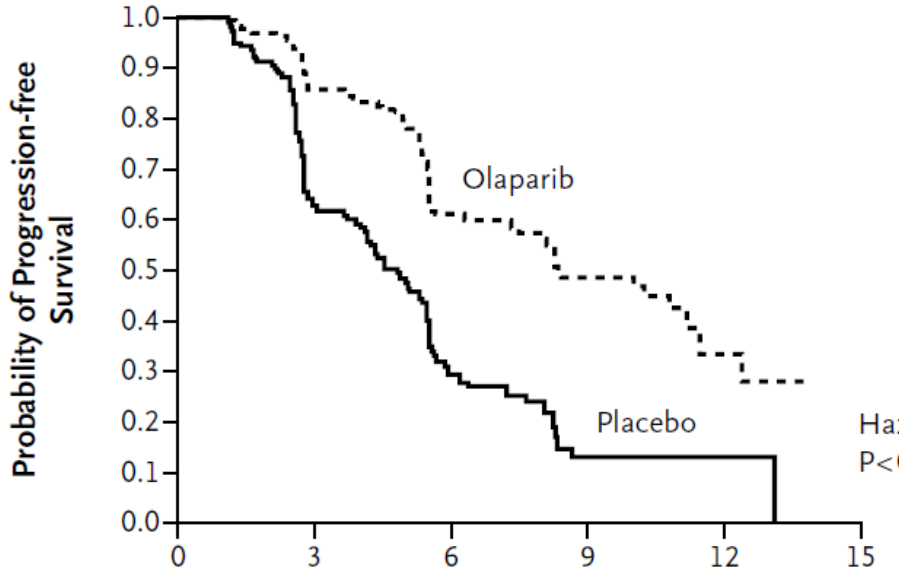
Lynparza

olaparib

The approved indication is: "monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy".

Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer

Ledermann J, N ENGL J MED 366;15 NEJM.ORG APRIL 12, 2012



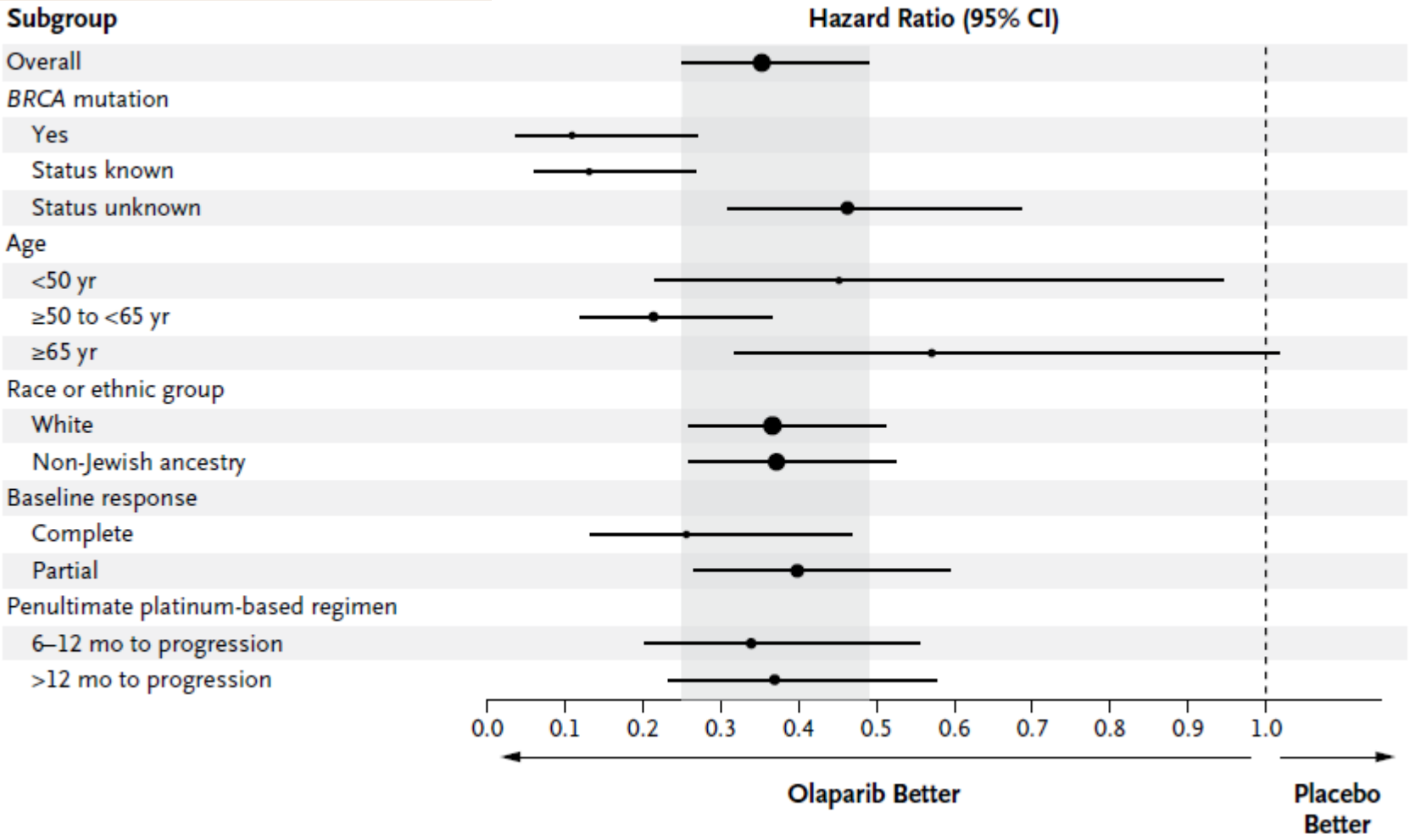
Hazard ratio, 0.35 (95% CI, 0.25–0.49)
P<0.001

No. at Risk							No. of Patients/ Total No. (%)	Median Progression-free Survival (mo)
Olaparib	136	104	51	23	6	0	60/136 (44.1)	8.4
Placebo	129	72	23	7	1	0	93/129 (72.1)	4.8

Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer

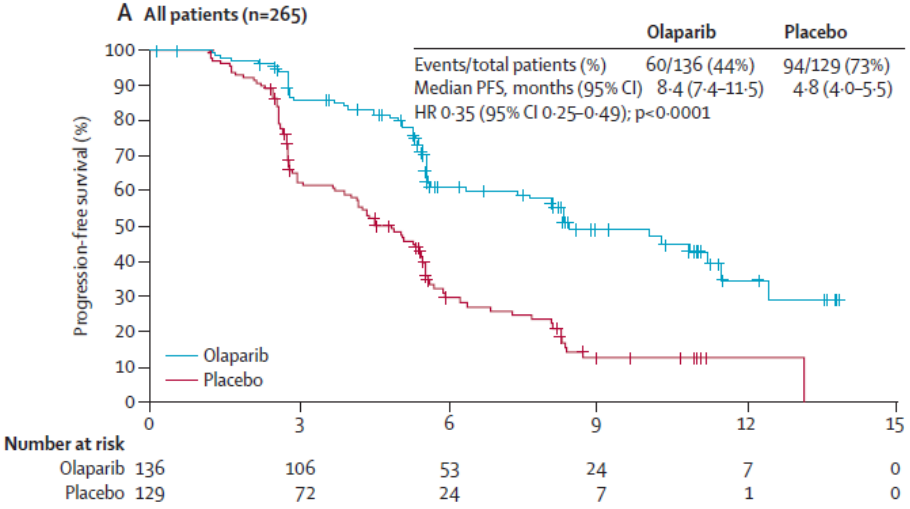
N ENGL J MED 366;15 NEJM.ORG APRIL 12, 2012

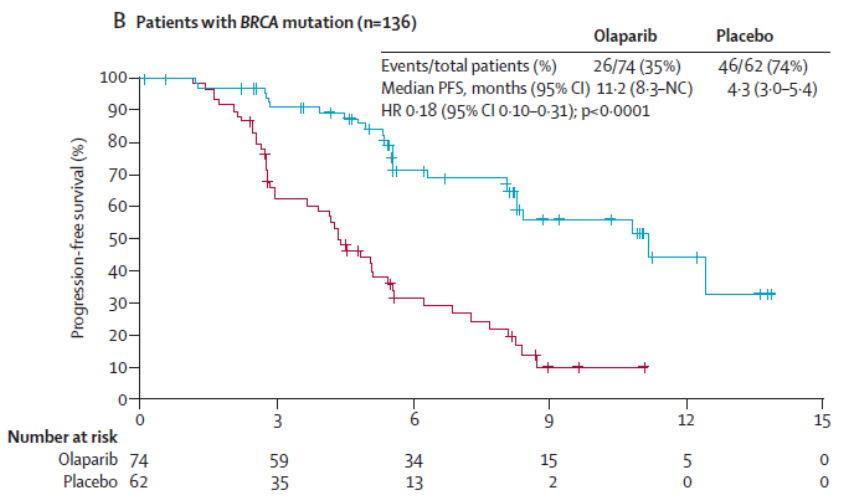
Subgroup Analysis of Progression-free Survival.

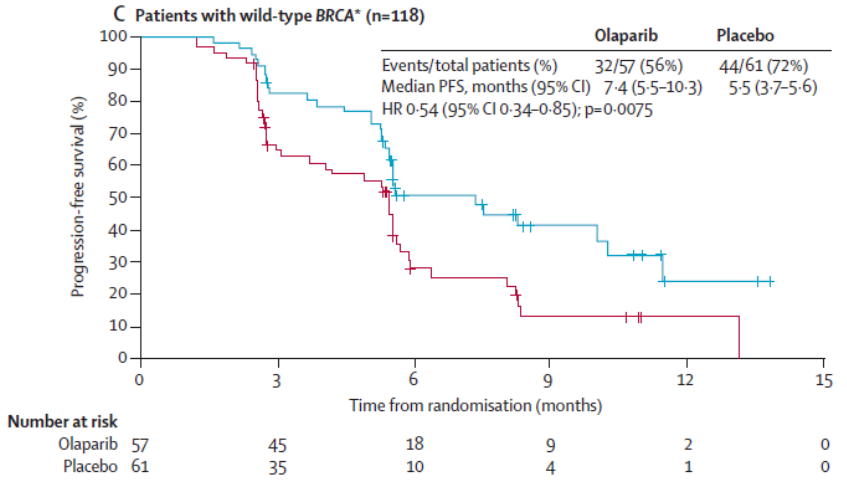


Subgroup analyses of PFS showed that, regardless of subgroup, patients in the olaparib group had a lower risk of progression than those in the placebo group. No predictive factors were identified (global treatment-by-subgroup interaction test, p=0.15).

Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by *BRCA* status in a randomised phase 2 trial



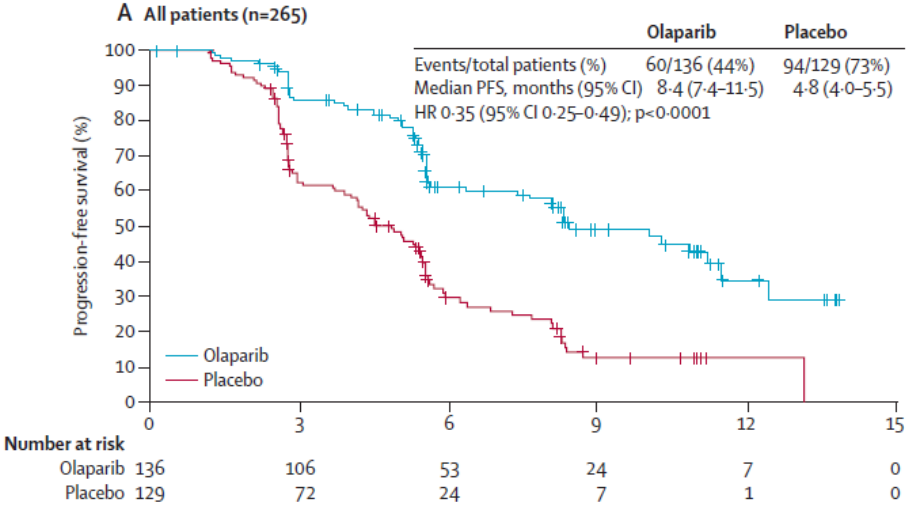


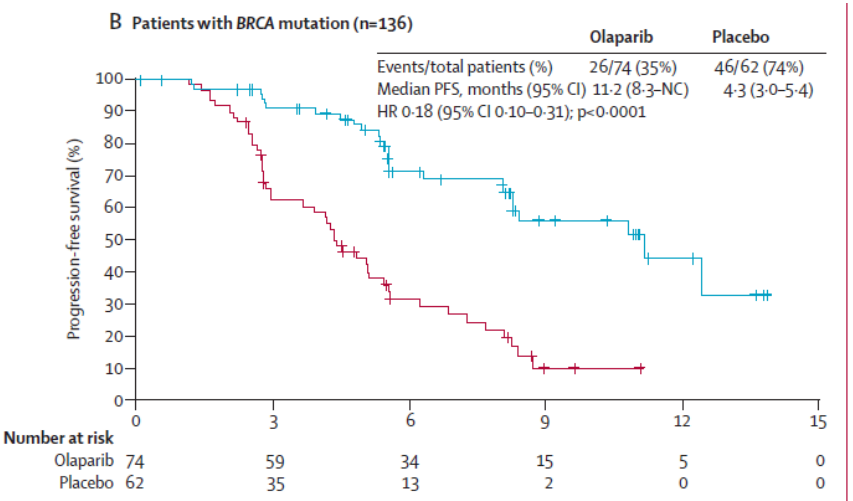


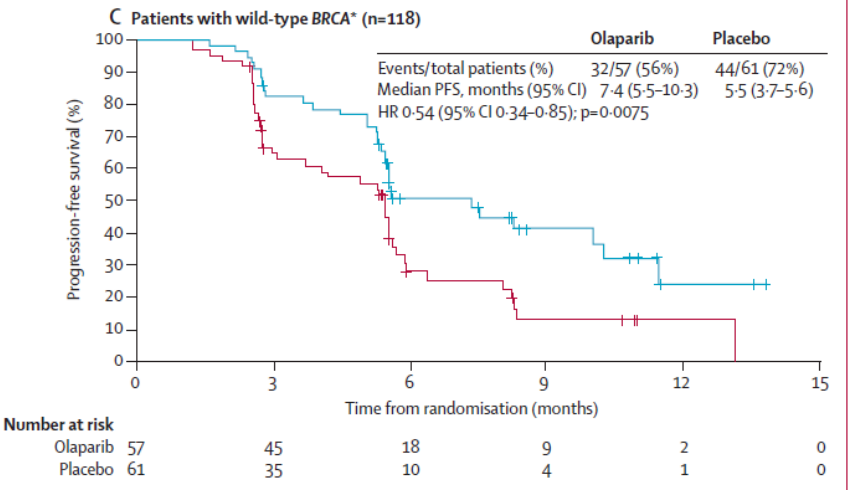
MI POSSO FIDARE DI QUESTI DATI?

Ledermann J, NEJM 2014; 15:852-61

Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by *BRCA* status in a randomised phase 2 trial







Questo “p value” , che abbiamo detto in precedenza NON deve essere mai indicato, può essere indicato in questo caso?

Ledermann J, NEJM 2014; 15:852-61

ICH Guideline E9

5.7 Subgroups, Interactions and Covariates

"In most cases…subgroup or interaction analyses are exploratory and should be clearly identified as such;…these analyses should be interpreted cautiously;…any conclusion of treatment efficacy (or lack thereof) or safety based solely on exploratory subgroup analyses are unlikely to be accepted."

S.L. George

Con il patrocinio di

AIOM

ONCOLOGIA AL FEMMINILE 2015

Un filo sottile per coniugare i progressi scientifici con la pratica clinica, le linee guida e l'etica

Coordinatore Scientifico
Stefania Gori

VERONA, Hotel Leon d'Oro - 18/19 Settembre 2015

Segreteria Scientifica

Laura Cortesi - Simona Duranti
Teresa Gamucci - Laura Scaltriti - Rosa Rita Silva

THANK YOU !

Ospedale **“SACRO CUORE -DON CALABRIA “ Negrar-VR**

Presidio Ospedaliero Accreditato- Regione Veneto